DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 17-525 / S-049
NDA 17-658 / S-035
NDA 18-039 / S-023

SEP 1 6 1998

Watson Laboratories, Inc.
Attention: Ron Lapre'
311 Bonnie Circle
Corona, CA 91720

Dear Mr. Lapre:

Please refer to your supplemental new drug applications dated February 12, 1998, received February 13, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Loxitane (loxapine succinate) capsules, Loxitane C (loxapine hydrochloride) liquid, and Loxitane IM (loxapine hydrochloride) intramuscular.

These supplemental applications provide for:

1. Incorporation of the following Drug Interaction text as a result of published case reports of adverse events following concomitant Loxitane/lorazepam therapy. Under PRECAUTIONS, immediately following the Information for Patients subsection, added:

   Drug Interactions
   There have been rare reports of significant respiratory depression, stupor and/or hypotension with the concomitant use of loxapine and lorazepam. The risk of using loxapine in combination with CNS active drugs has not been systematically evaluated. Therefore, caution is advised if the concomitant administration of loxapine and CNS-active drugs is required.

2. Incorporation of Pediatric Use text in compliance with 21 CFR 201.57 Labeling Content and Format guidelines. Therefore, the Usage in Children section is replaced with:

   Pediatric Use
   Safety and effectiveness of Loxitane in pediatric patients have not been established.

We note that these supplements were submitted as 'Special Supplement - Changes Being Effected' under 21 CFR 3 14.70(c) Your submission stated October 17, 1997, as the implementation date for the change(s).

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drugs are safe and effective

for use as recommended in the final printed labeling submitted on February 12, 1998. Accordingly, these supplemental applications are approved effective on the date of this letter.

Please note that the "Changes Being Effected" supplements of April 6, 1988, containing Final Printed Labeling (NDA 17-525/SLR-036, NDA 17-658/SLR-027, and NDA 18-039/SLR-016), have now been superseded and will not be reviewed, but they will be retained in our files.

Your "Content and Format" supplements of January 28, 1983 (submitted to each Loxitane NDA), have not been superseded.However, we note that your current labeling is formatted in the "spirit" of 2 1 CFR 201.57 and recommend that you amend your pending "Content and Format" submissions (i.e., pregnancy category, etc.) to bring the Loxitane products into full compliance with the regulation.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Steven D. Hardeman, R.Ph., Regulatory Project Manager, at (301) 594-5533.

Sincerely yours,

9/15/98

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research